Systematic Review/Meta-analysis

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Survival rate of vaginal cancer in Asian countries: a systematic review and meta-analysis

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Introduction: Vaginal cancer is one of the major causes of mortality in women, which mostly takes place in low- and middle-income countries. Assessing the survival rate of vaginal cancer is essential to investigate the success rate of current treatments and screening tools. This study aims to determine the survival rate of vaginal cancer in Asia.

Methods: This systematic review was carried out using four international databases, including Medline/Pubmed, ProQuest, Scopus, Web of Knowledge, and also Google Scholar. Articles were investigated up to the end of August 2021. The authors utilized the Newcastle–Ottawa Scale to evaluate the quality of the articles. Evaluating the papers for heterogeneity was performed using the Cochrane test and I^2 statistic. Meta-regression analysis was also applied based on the year of the study.

Results: Three articles (13 records) fulfilled the inclusion criteria. Based on the random model, the overall 5-year survival rate was 74.63%. Also, the rates of survival in relation to the type of treatment including chemotherapy, radiotherapy, or other modalities, were 78.53, 78.44, and 68.54%, respectively. According to meta-regression analysis, no correlation was found between the survival rate and the year of the study.

Conclusion: The vaginal cancer survival rate is lower in Asian countries compared to that of developed countries. Increasing patient survival rates in such countries is crucial by implementing newer diagnostic tools, advanced surgical techniques, and goal-oriented treatments. Early diagnosis in lower stages and educating the populations about risk factors and preventative measures are also necessary for raising the rate of survival.

Keywords: Asia, survival, meta-analysis, systematic review, vaginal cancer

Introduction

Malignancies are one of the most important causes of mortality and morbidity worldwide, only preceded by cardiovascular disease[1]. Gynecological malignancies involve the female genital tract, including ovarian, cervical, uterine, vulvar, vaginal, and gestational trophoblastic neoplasms. Gynecological neoplasms comprise a significant part of malignancies and have substantial mortality and morbidity rates[2]. According to the latest data released by Globocan in 2020, there is an incidence of 17908 vaginal cancers each year, and 7995 individuals die annually because of this cancer. The incidence and standardized incidence rate for this cancer were reported to be 0.46 and 0.36, respectively, and the mortality rate and standardized mortality rate were 0.21 and 0.16 per 100 000 population[3]. Vaginal cancer is a rare malignancy and makes up less than 2% of gynecological cancers worldwide[1]. The mortality rate in developing countries is 44.7 percent compared to 15.4 percent in developed countries[1]. Most cases of the invasive disease happen in women aged 60 and older, excluding adenocarcinoma, which occurs in younger patients[1,4]. Vaginal cancer is frequently diagnosed at an advanced stage and

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has a lower 5-year survival than vulvar cancer in the United States (39.8 compared to 79.3%, respectively)[5].

Multiple risk factors have been associated with vaginal cancer, especially the SCC (Squamous Cell Carcinoma) type, including cigarette smoking, immunocompromised state, multiple sexual partners, and a previous history of cervical precancerous and cancerous lesions. Vaginal adenocarcinoma, specifically clear cell adenocarcinoma, has been associated with in-utero exposure to DES (diethylstilbestrol), which was used as an antiabortive medication up until the beginning of the 1970s[4]. Different viral infections are involved in 15–20% of human neoplasms, such that some viruses play an essential role in developing malignant neoplasms. The correlation of a virus and its related neoplasm varies between 15 and 100%[6]. HPVs (Human papillomaviruses) are shown to be related to vaginal malignancies in a few case–control studies[4]. It is determined that chronic infection with this virus causes precancerous changes in the epithelial cells, which eventually leads to cancer in a matter of years. Vaginal cancers are developed through precancerous lesions termed VaIN (Vaginal Intraepithelial Neoplasm), but screening for this lesion is not recommended[1]. More than 200 different HPV genotypes have been recognized so far, and HPV types 16 and 18 account for 70% of vaginal cancers. Previous reports claim that 65–100% of the sexually active population are at risk of encountering HPV and its related cancers in their lifetime[7]. HPV vaccines are highly effective in preventing cancers related to this virus[8]. Massive HPV vaccination with high coverage will probably fight this burden, but the effect might take decades to take place[9].

Knowing the survival rate of vaginal cancer in Asia can give us valuable data in regard to control, prevention, and treatment consequences. However, more information is needed, given the rarity of this disease. There has not been a comprehensive and complete study on the matter in Asia yet, so this study was conducted to perform a systematic review and meta-analysis for determining the vaginal cancer survival rate in Asian countries and also to determine these rates regarding the type of treatment received.

HIGHLIGHTS

- The vaginal cancer survival rate is lower in Asian countries in comparison to developed European countries and the United States.
- Vaginal cancer is a rare disease, and there is currently no suitable screening tool for early detection.
- It is crucial to utilize existing knowledge to develop plans and policies specifically targeting the identification of high-risk individuals.
- High-risk individuals often possess well-studied risk factors such as HPV infection, having multiple sexual partners, and tobacco smoking.
- It is also much needed to conduct studies to determine the survival rates for vaginal cancer in other Asian countries.

Methods

Study registration and reporting protocol

The current study is a systematic review and meta-analysis of the vaginal cancer survival rate in Asia conducted in 2022. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis), Supplemental Digital Content 1, http://links.lww.com/MS9/A257 guidelines were followed for this study[10]. Also, this work has been reported in line with AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines, Supplemental Digital Content 2, http://links.lww.com/MS9/A258.

Search strategies

The researchers reviewed four international databases, including Medline/Pubmed, ProQuest, Scopus, and Web of Knowledge until the end of August 2021. We investigated Google Scholar for gray literature as well. Keywords used in our literature review included Vaginal Neoplasms [Mesh], Survival OR Survival Analysis OR Survival Rate, and Asian Countries (Names of countries). (Appendix 1, Supplemental Digital Content 3, http://links.lww.com/MS9/A259). The gathered information was imported into Endnote X7 software, and duplicate articles were removed automatically. It is of note that the articles were reviewed by two researchers independently. The search strategy is demonstrated in Appendix 1 (Supplemental Digital Content 3, http://links.lww.com/MS9/A259).

Inclusion/exclusion criteria

All observational studies (cross-sectional, case–control, and cohort) in English that were published by the end of August 2021 and mentioned vaginal cancer survival rate were incorporated in the study regardless of the time they were conducted. We excluded review studies and meta-analyses. It should also be noted that studies not mentioning the sample size and those that did not report the confidence interval of the survival rate were excluded from the meta-analysis.

Data extraction and study quality assessment

Data were extracted from all the final articles included in the study using a fore-made checklist. The checklist contained the author's name, year of publication, study period, sample size, country, 5-year survival rate, and the type of treatment received (chemotherapy, radiotherapy, and other treatments like surgery or a combination of different treatments). The primary search of the articles was performed by two researchers. The screening of the studies, data extraction, and quality assessment of the articles were also conducted by two researchers separately. If there were incongruence between the two researchers, then the team moderator would announce the final viewpoint about that article. For assessing the quality of the articles, we used the Newcastle–Ottawa scale, which is comprised of three parts: 1-selection (4 questions), 2-comparability (1 question), and 3-outcome (3 questions). It is divided into three groups based on the final score, which are Good, Fair, or Poor. Good- 3 or 4 stars in the selection part, 1 or 2 stars in the comparability part, and 2 or 3 stars in the result part. Fair- 2 stars in the selection part, 1 or 2 stars in the comparability part, and 2 or 3 stars in the result part. Poor- 0 or 1 star in the selection part, 0 stars in the comparability part, and 0 or 1 star in the result part[11].

Statistical analysis

We assessed study heterogeneity using the Cochrane test with a significance level set at less than 0.1 and the I^2 statistic. In cases where significant heterogeneity was observed among the included studies, we employed a random-effects model with the inverse-variance method to account for the variability. Additionally, to further explore potential sources of heterogeneity, we conducted meta-regression and subgroup analyses, considering relevant factors such as year, study design, and treatment modality. All statistical analyses were performed using STATA software version 16, MEDCALC 14, and Jamovi 2.3.12. We used appropriate statistical tests to calculate survival, CI, and *P*-values.

To assess publication bias, we planned to employ funnel plots and conduct Egger's regression test if a sufficient number of studies were available. However, due to the limited number of included studies, we were unable to perform a comprehensive analysis of publication bias.

Additional Analysis

Due to the high heterogeneity between the included studies, meta-regression analysis was also applied. The factor used in meta-regression analysis was the year in which the study was conducted.

Bias risk among studies

The random-effects model is used to decrease the risk of bias in the studies[12,13]. Egger's test was used to assess for potential publication bias as well[14].

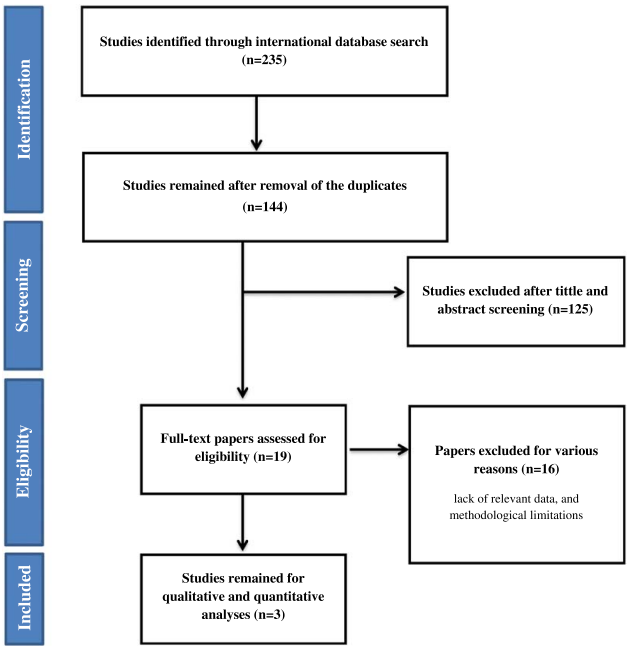

Figure 1. Flowchart of the included eligible studies in systematic review.

Results

Study selection

A total of 235 articles were found during the primary search of the international databases, and after removing repetitious ones, 144 articles were reviewed by their title and abstract. At this point, 19 articles entered the next phase, and their full text was reviewed; three articles (13 records) made it to the final analysis. The references of these articles were reviewed as well to add the relevant studies. The process of selecting the articles is demonstrated in Fig. 1.

Study characteristics

The selected articles were published between 2013 and 2017. Three articles in this period regarding the 5-year survival of vaginal cancer and its treatment in Asian countries fulfilled the criteria and were included in the study. One study from China, one from Japan, and one from South Korea were selected. Descriptive data from these studies are shown in Table 1.

Quality appraisal

The results of the quality assessment of the articles are demonstrated in Appendix 2 (Supplemental Digital Content 4, http://links.lww.com/MS9/A260). According to the quality assessment using the checklist that was mentioned earlier, all three studies possessed good quality.

Heterogeneity

The results of the χ^2-test and I^2 statistic showed considerable heterogeneity among the studies. The analysis showed the 5-year survival rate of vaginal cancer to be as follows: chemotherapy ($I^2 = 95.23\%$, $P \leq 0.001$), radiotherapy ($I^2 = 26.83\%$, $P \leq 0.222$), other treatments ($I^2 = 98.20\%$, $P \leq 0.001$) and overall ($I^2 = 96.63\%$, $P \leq 0.001$). For this reason, the random-effects model was used.

The overall 5-year survival rate in Asian countries

From the three final articles, including 13 records according to the random-effect model, the 5-year survival rate is determined to be 74.63% (95% CI: 64.36–84.90) (Fig. 2).

The 5-year survival rate was also determined based on the type of treatment.

The 5-year survival rate of chemotherapy for vaginal cancer in Asian countries

From all the included articles, five records reported the survival rate for chemotherapy; based on the random-effect model, the related survival rate was 78.53% (95% CI: 62.52–94.54) (Fig. 2).

The 5-year survival rate of radiotherapy for vaginal cancer in Asian countries

From all the final articles, three records reported the survival rate of patients who received radiotherapy, and based on the random-effect model, it is 78.44% (95% CI: 72.87–84.01) (Fig. 2).

Table 1

Basic information of included studies.

Order	Author (year)	location	Time period	Sample size	Treatment*	5-year survival rate	Quality assessment
1	Chang J.H. *et al.* 2016	Korea	1976–2011	138	Other treatment	68	7 (Good)
1	Chang J.H. *et al.* 2016	Korea	1976–2011	138	Radiotherapy	79.6	
1	Chang J.H. *et al.* 2016	Korea	1976–2011	138	Chemotherapy	47.8	
1	Chang J.H. *et al.* 2016	Korea	1976–2011	138	Other treatment	68.9	
2	Ikushima, H & *et al.* 2017	Japan	2000–2010	90	Radiotherapy	82.5	7(Good)
2	Ikushima, H & *et al.* 2017	Japan	2000–2010	90	Radiotherapy	71.4	
2	Ikushima, H & *et al.* 2017	Japan	2000–2010	90	Chemotherapy	79.3	
2	Ikushima, H & *et al.* 2017	Japan	2000–2010	90	Other treatment	75.8	
3	Tang Q.L *et al.* 2014	China	1995–2014	77	Chemotherapy	91.1	6(Good)
3	Tang Q.L *et al.* 2014	China	1995–2014	77	Other treatment	100	
3	Tang Q.L *et al.* 2014	China	1995–2014	77	Other treatment	28.6	
3	Tang Q.L *et al.* 2014	China	1995–2014	77	Chemotherapy	93.6	
3	Tang Q.L *et al.* 2014	China	1995–2014	77	Chemotherapy	80.2	

*Other treatment: chemoradiotherapy, external beam radiotherapy, Brachytherapy)other treatments except radiotherapy and chemotherapy).

The 5-year survival rate of other treatments for vaginal cancer in Asian countries

From all the final articles, five records reported the 5-year survival rate of other treatment regimens in patients, which based on the random-effect model is 68.54% (95% CI: 46.06–91.02) (Fig. 2).

The vaginal cancer survival rate in each Asian country

The results of the survival rate in these three countries are depicted in Fig. 3. The 5-year survival rates for vaginal cancer in China, Japan, and South Korea are 78.96% (95% CI: 53.78–100), 77.71% (95% CI: 73.10–82.32), and 66.21% (95% CI: 53.24–79.18), respectively.

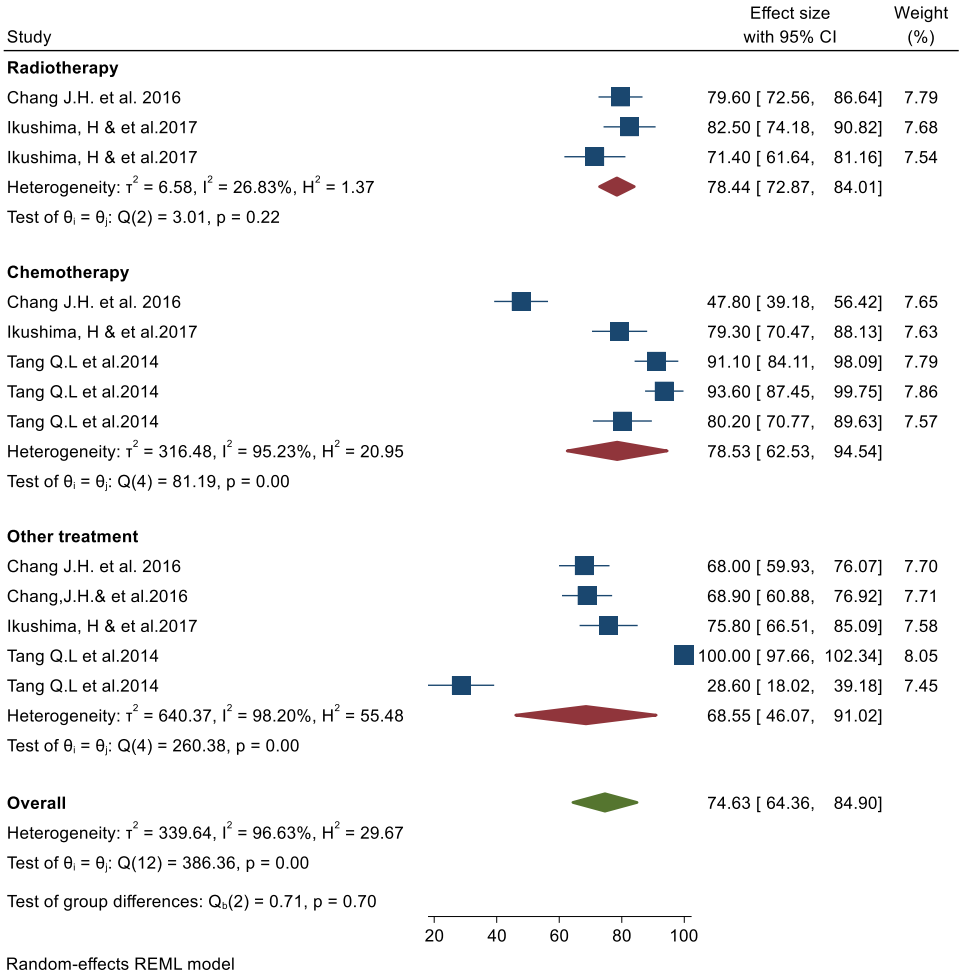

Figure 2. Forest plot of 5-year survival of vaginal cancer according to the type of treatment.

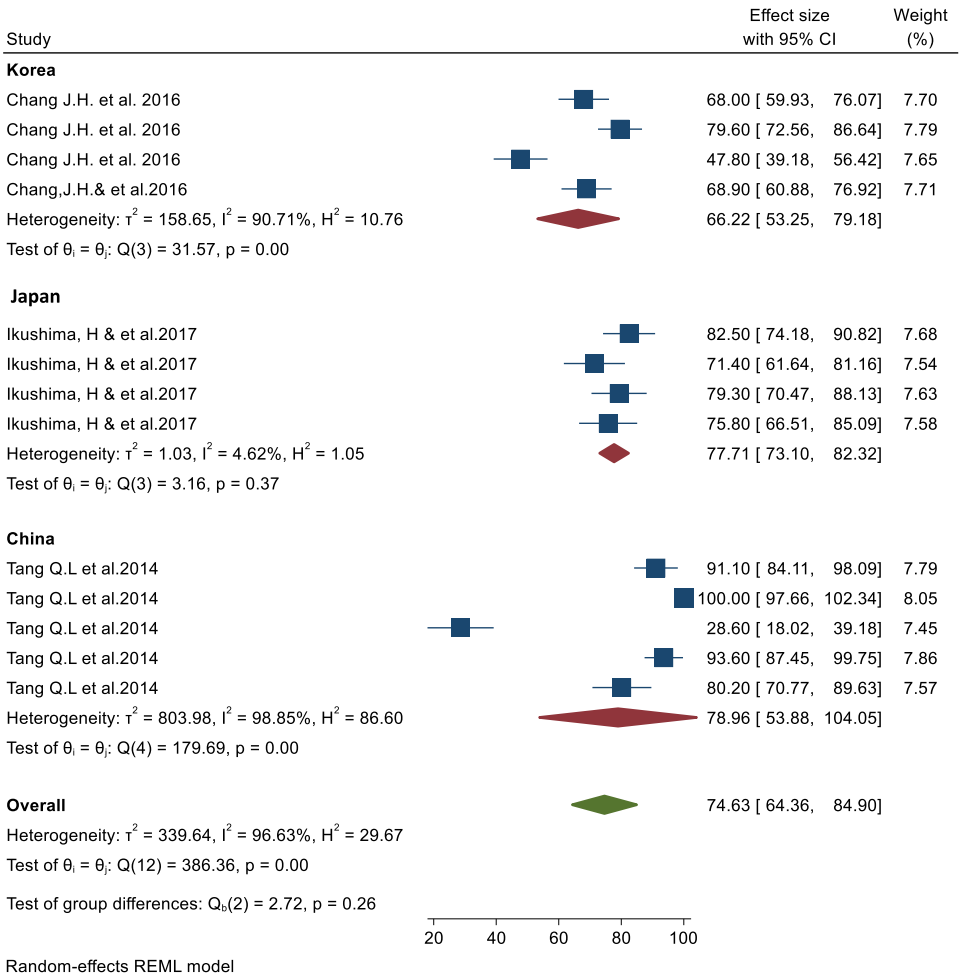

Figure 3. Forest plot of 5-year survival of vaginal cancer according to country.

Meta-regression of the vaginal cancer survival rate in Asian countries

There was no relation between the year of the study and the overall and treatment-related 5-year survival of vaginal cancer in Asian countries ($P > 0.05$) (Appendix 3, Supplemental Digital Content 5, http://links.lww.com/MS9/A261).

Publication bias

Funnel plots were drawn to investigate the publication bias for the overall and treatment-related 5-year survival rate of vaginal cancer in Asian countries, and the results of Egger's test confirmed this bias. (Overall bias: – 12.03%, SE = 3.76; $P = 0.0014$). (Appendix 4, Supplemental Digital Content 6, http://links.lww.com/MS9/A262).

Discussion

Vaginal cancer is one of the rare but bothersome cancers for women, which can bring about many psychological and marital issues in their lives[15]. The 5-year survival rate of vaginal cancer in Asian countries was investigated in the present study. Results from this study revealed that 5-year survival rates for vaginal cancer in China, Japan, and South Korea are 78.96, 77.71, and 66.21%, respectively. Also, no correlation was found between the overall survival rate and the year of the study or the type of treatment in Asian countries.

Similar to Asian studies, the 5-year survival rate of women with vaginal cancer in America regarding disease stage is reported to be 84 for stage 1, 75 for stage 2, and 57% for stages 3 and 4[16]. Also, the survival rate of patients with vaginal cancer in India was 30% for grades 3 and 4 tumors[17]. The stage of the disease can affect the treatment outcomes. New metastasis and resistance to treatment in the third and fourth stages of the disease will lead to recurrence[18,19]. As was demonstrated in one Indian study, the only contributing factor to disease recurrence was the stage of malignancy[17].

The study results revealed that there is no change in the survival rate of patients with time. This finding is contrary to Chirag's study in the United States, which showed that the survival rate decreased by 17% between 1990 and 2004[16]. In developed countries, people have had better access to health care over time, and with education about better lifestyle choices, they have managed to improve their health conditions. Furthermore, it is noted that early diagnosis plays a good prognostic factor in patients receiving radiotherapy[20].

Unfortunately, there is no proper screening tool for the detection of vaginal cancer in the early stages[21]. The lack of a proper screening tool could be why there has not been a change in early diagnosis and, consequently, no change in the survival rates over time. Also, the disease's low prevalence and difficulties in executing clinical trials[22] will result in a need for more valid information regarding the cause of this problem.

On the other hand, one study showed that differences in ethnicity, race, and patients' age would cause various vaginal cancer survival rates[23], such that Asian races with diverse genetic structures will have different outcomes regarding disease-fighting capacity and survival rates of patients. Due to the usage of more vigorous radiation therapy and higher radiation-related toxicity for larger tumor sizes, it is better to prevent treatment complications over time to augment the survival rate[24].

In the present study, it was claimed that there is no relation between the type of treatment and the survival rate in Asian countries. This finding is against other studies which show favorable treatment response with high-dose brachytherapy in grades 1 and 2 vaginal cancer, resulting in higher survival rates and reduced complications[25,26].

The mortality rate in patients experiencing advanced disease, squamous cell carcinoma, and adenocarcinoma who are receiving brachytherapy is also reduced[27]. Along with the treatment, other factors can affect the 5-year survival of vaginal cancer patients as cofounder, including HPV infection[28–30], tobacco smoking, an increased number of sexual partners, and the early onset of sexual activity[31]. The findings in this study are solely gathered from three studies in China, Japan, and South Korea, prompting the need to conduct more studies about vaginal cancer patients. Also, this study has several limitations that should be considered when interpreting the findings. Firstly, the sample size in each study was relatively small, which may limit the generalizability of the results to a larger population of vaginal cancer patients. Additionally, there might be a potential selection bias in participant recruitment, potentially affecting the representativeness of the study sample. Another limitation is the retrospective design in some studies, which could introduce biases in data collection and potential confounding variables that were not controlled for in the analysis. Moreover, the quality and reliability of the data used for the analysis could be subject to limitations, including missing data and inconsistencies in data collection methods. Variations in treatment protocols, such as different chemotherapy regimens or radiation therapy techniques, were not considered, which could impact treatment outcomes and survival rates. Lastly, despite efforts to control for confounding variables, there may still be unmeasured factors that could influence treatment outcomes and survival rates but were not accounted for in the analysis. These limitations highlight the need for caution when interpreting the results and suggest areas for further research to address these limitations and provide more robust evidence. Given the low prevalence of the disease and the difficulties of performing studies, it is essential to educate the population on alarm signs and to detect individuals at an early disease stage.

Conclusion

The vaginal cancer survival rate is lower in Asian countries in comparison to developed European countries and the United States. It is necessary to increase the survival rate by providing newer diagnostic tools, improved surgical techniques, goal-oriented treatments, and early disease detection. However, because this is a rare disease and we have no appropriate screening tool for its early detection, it is crucial to use the current knowledge to establish plans and policies focused on the detection of high-risk individuals having well-studied risk factors like HPV infection, having multiple sexual partners and tobacco smoking. It is also much needed to conduct studies to determine the survival rates for vaginal cancer in other Asian countries.

Ethical approval

The study was done after holding the ethical code of IR.MUBABOL.HRI.REC.1401.105 from Babol University of Medical Sciences. Written informed consent was obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations of the Declaration of Helsinki.

Consent

Not applicable. This article is a systematic review study.

Sources of funding

The study was reviewed and approved by Medical Ethics Committee of Babol University of Medical Sciences.

Author contribution

H.A.N, M.V., and Z.M.: conceived and designed the study; M.A. J, A.S., M.V., S.H., S.S., and M.J.: collected the data; H.A.N, S.H., M.H.V., S.N.H., and M.G.G.: analyzed the data; M.J., M. A.J., and S.H.: wrote the paper; A.K.: revised the paper; M.G.G.: supervision; H.A.N.: approval of the final manuscript. The decision to submit this manuscript for publication was jointly made by all authors and the manuscript was confirmed to be accurate and approved by all authors.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interests.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Hossein-Ali Nikbakht: Corresponding author.

Data availability statement

The datasets are available from the corresponding author on reasonable request.

Provenance and peer review

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